# A CASE OF BLACKWATER FEVER FOLLOWED BY A PECULIAR RELAPSE WITHOUT HAEMOGLOBINURIA OR DETECTABLE *PLASMODIA*

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This case was studied under the conditions and by the methods referred to in the previous paper, and is, we believe, the first case of blackwater fever which has occurred while daily estimations of the numbers of *Plasmodia* were being made by thick film methods. Though there is much evidence to connect blackwater fever with malaria, yet many authors doubt whether the typical fever generally associated with the haemoglobinuria is due entirely or at all to the parasites of malaria. Our case is of special interest because it throws considerable light on this question. It will be seen from the chart that the case had three separate pyrexial periods while under observation; that the first of these was an ordinary malarial attack; the second an ordinary blackwater attack (without detectable parasites); and the third a singular attack during which neither blackwater nor parasites were found—strongly suggesting, if not proving, that the later attacks were due to some cause other than the toxin of the *Plasmodia*, and that haemoglobinuria may be merely an occasional result of this unknown cause. A fourth attack occurred still later but, unfortunately, could not be studied by us.

The patient, A. E. B., male, aged 32, an English trader on the Gold Coast since 1903, stated that he had slight fever during his first year in West Africa, and numerous slight or severe attacks since then, but without any observed blackwater fever. He did not take much quinine until more recently, when (in February, 1910) he was given 30 grains daily for a fortnight, without its producing blackwater. He was admitted to the Royal Southern Hospital,

Liverpool, on the 2nd June, 1910, owing to the continuance of such attacks. His weight was 114 pounds (52 kilograms); he looked pale, thin and anaemic; his liver was enlarged half an inch below the costal margin, but his spleen, though enlarged, was scarcely palpable.

As shown on the chart, on the day of admission 2,600 asexual forms of *Plasmodium falciparum* were found per c.mm. of his blood accompanied by the usual fever. On the following five days the same parasites numbered 80, 1,360, 880, 20, and 12 per c.mm., accompanied by fever on the 2nd, 3rd, and 4th days after admission. Quinine hydrochloride (10 grains) was given on the 4th day and 30 grains daily until the 10th day inclusive. No parasites were found on the 7th and 8th days, and no fever occurred on the 5th, 6th, 7th and 8th days. On the 7th and 8th days he was allowed out of hospital for a few hours in the afternoon, and on the latter day got heated with exercise, and ate ices.

On the 9th day he was attacked with high fever with rigors. On the 10th day haemoglobinuria commenced and the quinine was stopped. The attack was very serious. The haemoglobinuria cleared up on the evening of the 11th day, but the fever continued to a diminishing degree until the 18th day, though the temperature occasionally rose slightly above normal until the 37th day. There was then a break for four days, on the last of which he was again allowed out of hospital. On the 42nd day another severe pyrexial period commenced, lasting until the 54th day, but not accompanied by any haemoglobinuria. The patient now improved greatly and was discharged on the 63rd day; but returned again to hospital on the 76th day with fever (which, however, was not examined by us), but no blackwater. The parasites were carefully searched for (by D. T.), both in thick and thin films, on forty days up to the 49th day of the disease, after which, unfortunately, the examinations could not be continued. On not a single occasion since the 6th day of the disease could a single *Plasmodium* be found, though during the 9th, 10th and 11th days, that is, during the blackwater period, the blood was examined by both methods four times daily. No crescents were ever seen.

It should be noted that the haemoglobin of the blood, estimated (by D. T.) by Sahli's haemoglobinometer, began to fall on the 8th

day, the day before the fever of the 9th day commenced, and fell 10 per cent. daily during the next four days—the total fall being from 75 to 25 per cent. during seven days. It remained at the latter figure and then rose by about 5 per cent. daily for four days, and then more slowly. A slight fall interrupted the continuous rise on the 29th day, but on the 40th day the haemoglobin had reached 90 per cent. During the second relapse, occurring on the 42nd day, it underwent a total fall of only 12 per cent.

The red cells varied as follows:—

| Days ... ... | 11 | 12 | 14 | 18 | 20 | 21 | 22 | 25 | 29 |
|---|---|---|---|---|---|---|---|---|---|
| Numbers in thousands | 2,600 | 1,150 | 800 | 1,450 | 1,600 | 1,900 | 2,000 | 2,500 | 2,800 |

Regarding the urobilin (G. C. E. S.), there was only a very slight rise in the urinary excretion, reaching a maximum of 63 mgms. during the first febrile period. During this time two observations of the faecal excretion disclosed a total of 1,836 mgms. Commencing from the 10th day the faeces were examined continuously, and disclosed a urobilin excretion of 32,500 mgms. during six days, falling after this to the low figure of 100 mgms. per diem. During the blackwater period there was a marked degree of urinary urobilin, namely, 340 mgms. on the 10th day, 300 mgms. on the 11th day and 115 mgms. on the 12th day—after which it fell to the low level of 30 to 60 mgms. a day. The actual quantity of haemoglobin in the urine was estimated in each sample passed during the period of blackwater, and reached its height at 7 p.m. on the 10th day, and then fell gradually as follows:

10TH DAY

| Hours ... ... ... ... ... ... ... ... | 10 a.m. | 7 p.m. | 11 p.m. |
|---|---|---|---|
| Quantity of urine ... ... ... ... ... ... ... | 95 c.c. | 90 c.c. | 200 c.c. |
| Amount of Hbg. (expressed as red blood cells by volume) ... | Trace | 4·5 c.c. | 0·5 c.c. |

11TH DAY

| Hours ... ... ... ... ... | 2 a.m. | 9 a.m. | 12 noon | 7 p.m. | 9 p.m. |
|---|---|---|---|---|---|
| Quantity of urine ... ... ... | 250 c.c. | 110 | 200 | 625 | 360 c.c. |
| Amount of Hbg. (expressed as red blood cells by volume) ... ... ... | 0·625 c.c. | 0·055 c.c. | 0·33 c.c. | 0· | 1·98 c.c. |

12TH DAY

| Hour ... ... ... ... ... ... ... ... ... ... ... | 3.30 a.m. |
|---|---|
| Quantity of urine ... ... ... ... ... ... ... ... ... ... | 570 c.c. |
| Amount of Hbg. (expressed as red blood cells by volume) ... ... ... ... | 0· |

In all, the haemoglobin of 17 c.c. of normal blood or about 25 grains of haemoglobin was passed unaltered in the urine.

We should note that during the blackwater period and subsequent fever up to the 23rd day, chlorides were markedly diminished in the urine and the specific gravity was rather low.

During the febrile periods beginning on the 9th and on the 42nd days there was no scarcity of leucocytes such as occurred during the first febrile period, or such as occurs during ordinary malarial febrile periods; but the mononuclear percentage was high all through, as occurs during malarial fever and afterwards. Much bilious vomiting occurred on the 10th and 11th days, and unaltered bile pigment was present in the faeces up to the 15th day. The patient had the usual jaundiced appearance during the second febrile period.

Quinine, which had been stopped since the 10th day, was resumed in doses of one grain daily on the 35th day and two grains daily from the 41st to the 46th day, when it was stopped again on account of the second relapse. The urobilin was not estimated during the third pyrexial period.

On studying the case, we observe that the first pyrexial period from the 1st to the 4th day accorded exactly with our previous experiences with the thirty-three ordinary cases of malaria described in our first paper ('Enumerative Studies on Malaria'). The amount and type of fever, number of leucocytes, fall of haemoglobin, amount of urobilin excretion, and effect of quinine were precisely what we would have expected from the number of parasites counted; and the same thing may be said of the following apyrexial period. But the subsequent events differed markedly from our previous experiences. Although no parasites whatever were found in numbers of thick film preparations, yet the fever, fall of haemoglobin, and urobilin excretion in the later febrile periods were so severe that they would usually be associated with, say, 50,000 parasites or more per c.mm. The type of fever in these periods also differed from that of the first period and from that seen in our cases of malaria. During the second period (of the 9th day) the fever consisted of several severe paroxysms on each day, accompanied by sharp rigors and profuse sweats—all of these much more severe and continued than are usually seen in old cases of malaria, even with very many parasites. The third pyrexial period was very similar to the second one, except only

that it was not so severe, and that haemoglobinuria was entirely absent. Moreover, the whole comparatively fever-free period from the 18th to the 41st day, in which the temperature frequently exceeded normal, differed from ordinary malarial apyrexial periods, in which the temperature generally remains quite and even considerably below normal, and asexual parasites are often still to be found. Quinine certainly did not prevent the second and third pyrexial periods, although it was never followed by relapses in our cases of malaria; and the leucocytes did not show the characteristic diminution of malaria.

From these facts we are inclined to infer, almost with certainty, that the second and third pyrexial periods were not due to the toxin of the parasites of malaria, that is, to the usual cause of malarial attacks, but to some other cause. As shown in our previous paper, the fact that parasites were not found in no less than forty-three thick film specimens does not prove by any means that none were present in the whole body; but it proves that their numbers were much below the usual figure required to produce even slight fever. If, then, the later pyrexial periods were due to the small remainder of parasites, either the 'virulence' of these must have become suddenly and greatly exalted after the 9th day, or else the patient's resistance to their toxin must have become suddenly lowered. Neither of these appears probable, because the general type of the fever in the later periods differed so much from the usual malarial type, and because quinine had no reducing effect. If there is another cause, as seems to be highly probable from this case, it must exert a powerful haemolytic as well as pyrogenous effect. The third pyrexial period is of great interest, because it appears to establish a new fact, namely, that this peculiar fever, though generally associated with a great fall of haemoglobin and also with haemoglobinuria, need not necessarily be associated with either (the *Plasmodia* being at the same time undetectable). This proves also that mere haemoglobinuria by itself does not cause the fever.

We now content ourselves with merely recording the observed facts without discussing the possible causes of the fever. Further researches are required to ascertain whether similar phenomena occur in other cases. It has been often shown since Panse's* researches

* Otto Panse. Zeit. fur Hygiene, 1902.

that the parasites tend to disappear at the onset of blackwater—but not, we think, so conclusively as in this case; nor do we know of relapses without either *Plasmodia* or haemoblobinuria having been previously noticed.

We should add (1) that no signs of any other parasites besides *Plasmodia* were seen; and (2) that the total elimination of urobilin from the 8th to the 15th day represents an amount of haemoglobin equal to that of *all* the patient's corpuscles, the 25 per cent. of haemoglobin still remaining being probably contained in young corpuscles generated during the period referred to. The relation between the numbers of circulating corpuscles and the haemoglobin percentage appears to confirm this estimate. As the asexual parasites cannot live outside the red corpuscles, this enormous destruction of the latter probably causes an equally great destruction of the former, which may explain Panse's law and the absence of parasites after the sixth day in our case; but it does not seem capable of explaining the fever. (3) The comparatively slight fall of haemoglobin during the third pyrexial period may be explicable on the supposition that the red corpuscles were then probably younger and more resistant. (4) The enlargement of the liver and the bilious vomiting might suggest derangement of the hepatic system, but they may also represent the hyperaemia of extreme activity. The fact that the liver eliminated, in its usual manner, such an enormous amount of blood pigment tends to confirm the latter hypothesis. (5) In conclusion, we would remark that haemoglobinuria seems to be merely a small overflow of the freed haemoglobin which the liver has not been able to deal with; and that some other cause other than the toxin of the *Plasmodia* seems to produce both the special haemolysis and the special fever associated with it.